STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 177312

TO: Anand Desai **Location: 3b69 / 3c70** **Art Unit: 1653** **Thursday, February 09, 2006** **Case Serial Number: 10 / 639999**	**From: Noble Jarrell** **Location: Biotech-Chem Library** **Rem 1B71** **Phone: 272-2556** **Noble.jarrell@uspto.gov**

Search Notes

ubiquitylation and determining whether the compound affects Type I-III ***N-end rule ubiquitylation***.
Making a pharmaceutical formulation containing one or more active compounds identified by the method of (7) comprises forming a mixture comprising the protein or an activated fragment of the protein having an exposed ***N-degron***, an ***N-end rule ubiquitylation*** system, one or more candidate compounds and, optionally, a proteosome system, detecting N-rule ubiquitylation and/or proteosome-mediated degradation of the compound, identifying one or more active compounds from the one or more candidate compounds and incorporating at least one of the one or more active compounds into a pharmaceutical formulation comprising at least one active compound and a carrier. The one or more active compounds are inhibitors or promoters of ***N-end rule ubiquitylation***. The one or more active compounds are naturally occurring. The one or more candidate compounds are selected from a compound library of FDA approved drugs. Modulating N-rule ubiquitylation of a protein comprises administering one or more active compounds of the methods of (7) - (9). Changing the level of a protein, e.g. aprataxin, tau, SLP, HMG17, PinX1, CIR, Cullin 3, HMGN3, HSPC144, CDC6 (in vitro, in vivo or ex vivo) comprises administering an amount of an active compound identified by the method of (7). Creating a modified protein by modifying a protein of interest to change its susceptibility to N-end rule degradation, the protein is aprataxin, tau, SLP, HMG17, PinX1, CIR, Cullin 3, HMGN3, HSPC144, CDC6 comprises decreasing the susceptibility of the protein to N-end rule degradation by modifying a protease cleavage site to prevent protease cleavage at the site, where cleavage at the protease cleavage site leads to exposure of an ***N-degron***, increasing the susceptibility of the protein to N-end rule degradation by introducing a protease cleavage site for a known protease, where cleavage at the protease cleavage site leads to exposure of an ***N-degron*** and decreasing the susceptibility of the protein to N-end rule degradation by modifying a protease cleavage site that when cleaved exposes an ***N-degron*** so that, after modification, the C-terminal product of the protease cleavage is not recognized by an N-end rule E3 ligase. The method further comprises expressing the modified protein in a cell. The cell does not express the protein of interest. Generating a phenotypic cell line or animal comprises generating a clone for a mutated form of a protein, e.g. aprataxin, tau, SLP, HMG17, PinX1, CIR, Cullin 3, HMGN3, HSPC144, CDC6 or their fragments or derivatives, the mutated protein having a mutated protease cleavage site and/or ***N-degron***, thus, modulating the susceptibility of the protein to ***N-end rule ubiquitylation***, using the vector to transfect the cell line or to generate a transgenic animal by homologous or non-homologous recombination and detecting at least one phenotypic change relative to a control cell line or animal expressing the non-mutated form of protein.

```
=> d his

     (FILE 'HOME' ENTERED AT 06:14:48 ON 09 FEB 2006)

     FILE 'HCAPLUS' ENTERED AT 06:15:24 ON 09 FEB 2006
L1             1 US2004137597/PN OR (US2003-693999# OR US2002-422448# OR US2003-
                 E DAVYDOV I/AU
L2           288 E3-17,E19-22
                 E KENTEN J/AU
L3            50 E3-7
                 E BIEBUYCK H/AU
L4            68 E3-7
                 E OBEROL P/AU
                 E OBEROI P/AU
L5             5 E3-4
L6            21 ((MESOSCALE OR MESO (1W)SCALE)(L)TECH?)/CS,PA
```

```
     FILE 'REGISTRY' ENTERED AT 06:20:01 ON 09 FEB 2006

     FILE 'HCAPLUS' ENTERED AT 06:20:03 ON 09 FEB 2006
L7             TRA L1 1- RN :       29 TERMS

     FILE 'REGISTRY' ENTERED AT 06:20:03 ON 09 FEB 2006
L8           29 SEA L7
L9         3885 ?UBIQUITIN/CNS
L10          41 APRATAXIN/CNS

     FILE 'HCAPLUS' ENTERED AT 07:14:37 ON 09 FEB 2006
L11           9 L10
L12          30 APRATAXIN
L13          33 L11-12
L14        2119 PROTEIN#/CW (L)(SLP# OR SYNAPTOTAGMIN (1W)LIKE (1W)PROTEIN# OR
L15         608 PROTEIN#/CW (L)(CULLIN3 OR CULLIN 3 OR CDC53 OR CDC 53 OR CULLI
L16           3 PROTEIN#/CW (L)(HSPC144 OR HSPC 144)
L17          25 PROTEIN#/CW (L)APRATAXIN
                E TAU FACTOR/CT
                E E3+ALL
L18        3460 E2+OLD
                E TRANSFERRIN/CT
                E E3+ALL
                E E2
                E E3+ALL
L19         227 E7+OLD,NT (L)TAU
L20       15063 ?UBIQUITIN
L21           5 L13-14,L16-17 (L) L19-20
L22         167 L15,L18,L19 (L) L20
L23         111 L13-14,L16-17 AND L9
L24         409 L15,L18,L19 AND L9
L25          15 L21-22 (L) CONJUGAT?
L26         165 L23-24 AND CONJUGAT?
L27           1 L25-26 AND L1-6
L28         127 N (L)END (L)RULE?(L)UBIQUIT?
L29           2 L25-26 AND L28
L30          28 N (L)DEGRON
L31           1 L30 AND L25-26
L32           1 L29,L31 AND L1-6
L33           1 L29,L31 NOT L32
L34           1 L31-33 AND L1-6
L35           2 L31-33 AND L11-30
L36           2 L34-35

     FILE 'MEDLINE' ENTERED AT 09:06:58 ON 09 FEB 2006
L37          19 N (1W)(DEGRON OR END (1W)RULE (1W)UBIQUIT?)

     FILE 'EMBASE' ENTERED AT 09:12:20 ON 09 FEB 2006
L38          19 L37

     FILE 'BIOSIS' ENTERED AT 09:16:13 ON 09 FEB 2006
L39          27 L38

     FILE 'WPIX' ENTERED AT 09:20:58 ON 09 FEB 2006
L40           6 L37
                SEL AN 2 L40
L41           1 E1 AND L40

=>
```